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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,039	12/05/2003	James A. Williams	D-2939CIPCONDIV4	5294

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,039	WILLIAMS, JAMES A.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/11/05 has been entered.

The Examiner of Record has changed from Virginia Portner to Jennifer Graser.

Claims 25-28 and 31 are currently under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102(e)

2. Claims 25-28 and 31 remain rejected under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994) for reasons of record and responses set forth below.

Response to Applicants' Arguments

Applicants argue that the claims differ from the product taught by Dolly because the instant claims recite that the C-terminal portion of the protein is obtained from *aerobic* bacteria as a single chain polypeptide. They argue that since Dolly teaches a C-terminal portion of the botulinum toxin which is obtained from Clostridial bacteria

(which is not an aerobic bacteria) it does not read on the instant claims. These arguments have been fully and carefully considered but are not deemed persuasive.

The instant claims are a product-by-process claim. "The patentability of a product does not depend upon its method of production. If the product in [a] product-by-process claim is the same as or obvious from a product of the prior art, [then] the claim is unpatentable even though the prior [art] product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983).

Applicants argue that the use of the limitation being produced as a 'single chain polypeptide' distinguishes over Dolly et al. This argument has been fully and carefully considered but is not deemed persuasive. It was well known in the prior art at the time the invention was made that toxins B, E and F naturally are produced as single chain polypeptides. See Bibhuti et al. Infection and Immunity. 1971. 6(4): 587-590. Dolly et al disclose the instant claimed invention directed to a recombinant botulinum neurotoxin wherein the botulinum toxin is botulinum toxin B, C, D, E, F and G. The botulinum toxin comprises a light chain portion), a heavy chain targeting portion and an internalizable portion (see Dolly et al, claim 4, and col. 5, lines 12-14) which are equivalent portions to

the C-terminal and N-terminal portions of a botulinum heavy chain. (Instant claim 27) The recombinant botulinum toxin is expressed using a maltose binding protein (see col. 17, lines 29-39) expression vector (see Dolly et al, for example: col. 3, lines 54-66) and would therefore evidence a specific solubility conferred by the expression vector fusion protein. (Instant claim 28) The botulinum toxin is claimed as a pharmaceutical composition (see Dolly et al claim 4) and is in solution with a pharmaceutically acceptable excipient (see Dolly et al, col. 41, lines 66-67).
The C-terminal and N-terminal portions of the heavy chain are linked one to the other (see Figure 1B), e.g., single chain polypeptide. The light chain and N-terminal of the heavy chain are bonded to each other (see figure 1B). No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The botulinum toxin is disclosed to be mutated through the addition of a non-toxin sequence, specifically a "cysteine" at the N-terminal of the light chain (see Dolly et al, col. 12, lines 55-61). An additional embodiment disclosed is the expression of the recombinant light chain as a fusion protein that comprises "a non-toxin protein sequence" that is cleavable by Factor Xa (see Dolly et al col. 28, lines 59-64,. figure 1A) or is a GST fusion protein (see Dolly et al, Example 21, col. 3 1).

Dolly et al anticipates the instantly claimed invention as now claimed.

Ledoux et al (1994) was previously cited to show and to provide evidence that botulinum neurotoxins are water soluble toxins (see abstract, page 1095, Ledoux et al).

Additionally, it is the position of the examiner that Dolly et al does disclose the use of "both native and recombinant wild-type Clostridial neurotoxin proteins (see col. 7, lines 32-35) as transporters which includes botulinum neurotoxin heavy chains (see col. 7, lines 32-35) that comprise the C-terminal fragment (heavy chain targeting portion, Dolly et al, claim 4, and col. 5, lines 12-14). While the reference does not exemplify this embodiment, the reference does constructively reduce this embodiment to practice for botulinum toxins B, C,D,E, F, and G (see Dolly et al, col. 7, lines 18-30, and col. 41, claims 2-3).

The recombinant expression of the Clostridial neurotoxin proteins are disclosed for expression in E.coli (see Dolly, col. 5, lines 38-52), which is a bacteria that grows under aerobic conditions.

While the instant claims recite the process limitation of "recombinant" no structural or functional characteristics that are not naturally present in the native neurotoxin protein are claimed. While the term "recombinant" shows the hand of man, the resultant structure of the recombinant protein is identical to that of the native neurotoxin protein, as no distinguishing sequences, amino acid sequences or post-translational modifications have been set forth in the claims. Dolly et al still anticipates the instantly claimed invention as now claimed.

Applicant asserts that compositions of Dolly et al comprise a recombinant light chain and uses MBP in the formation of the botulinum toxin and the present claims are directed to composition that comprise the C-terminal portion of a heavy chain of botulinum toxin.

It is the position of the examiner that Dolly et al's compositions comprise the C-terminal portion of a heavy chain (see Dolly et al col. 7, lines 32-35, that comprise the C-terminal fragment,(heavy chain targeting portion, Dolly et al, claim 4, and col. 5, lines 12-14) of botulinum toxin (see Dolly et al, col. 7, lines 18-30, and col. 41, claims 2-3). Applicant's compositions do not exclude the presence of additional botulinum neurotoxin chains and therefore still read on the compositions disclosed in Dolly et al for reasons of record and responses set forth above.

Claim Rejections - 35 USC § 102(a)

3. Claims 25-28 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by WO94/21684 for reasons of record and responses set forth below.

Response to Applicants' Arguments

Applicants argue that the addition of the limitation 'produced as a "single chain polypeptide" renders the rejection moot. This argument has been fully and carefully considered but is not deemed persuasive. W094/21684 disclose the instantly claimed invention directed to a composition that comprises a peptide portion of the heavy chain Hn together with a light chain (see Example I , page 7, L- Hn , the peptide evidencing an epitope present in botulinum toxin B, C and F (see Table 6, page 20). The C-terminal portion of the L-chain is covalently linked to the N-terminal portion of the heavy chain, e.g., single chain polypeptide. An additional embodiment disclosed comprises botulinum toxin heavy and light chains of serotypes B, C, D and E, the heavy chains comprising portions of both the Hn and Hc together with the N-terminal peptide that is held in

common with serotypes B, C and F (see Table 6, Expt. 2) and a solution (pharmaceutical excipient) carrier (see page 5, paragraphs 1-3 and claim 13- 14). No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" and "aerobic" limitations would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The polypeptide portion is disclosed to be in association with other non-toxin protein sequences, in a" conjugated or otherwise linked to other sequences" (see page 3, paragraph 4). Page 5, paragraph 1-3, Experiment 2, Table 6, page 20 and claims 13-14, WO94/21684 disclose a composition that comprises botulinum toxin heavy chains of serotypes B, C, D and E, the heavy chains comprising H_C receptor binding domain for serotypes B, C and F (see Table 6, Expt. 2), wherein the neurotoxin protein was in solution (pharmaceutical excipient) carrier (see page 5, paragraphs 1-3 and claim 13-14). Ledoux et al (1994) is being cited to show and to provide evidence that botulinum neurotoxins are water soluble toxins (see abstract, page 1095, Ledoux et al) and therefore would be a soluble botulinum toxin.

No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" and "aerobic" limitations would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The reference still anticipates the instantly claimed invention.

Double Patenting

4. Claims 25-28 and 31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 10 of U.S. Patent No. 5,919,565 in view of Williams et al (US Pat. 5,601,823).

Claim 10 of 5,919,565 is directed to genus of a fusion proteins of a Clostridium botulinum C fragment (abstract, first sentence) linked to a polyhistidine tract (tag) which is defined to include any serotype of A-G (' 665, col. 4, lines 28-43) and the instantly claimed invention is directed to specific serotype species, specifically types B, C1, D, E, F and G. The instant claims differ from the claims of 5,919,565 by not possessing a poly-histidine tag.

Williams et al teaches the production of recombinantly produced clostridium (botulinum and difficile(see col. 3, lines 25-29)) toxins as single chain polypeptides (see col. 8, lines 13-22, lines 59-63) either through coupling the toxin to a maltose binding protein polypeptide or to a polyhistidine tract polypeptide (see col. 35, lines 26-49, Example 11) in an analogous art for the purpose of producing large quantities of recombinant toxins for formulation of vaccines and generation of neutralizing antibodies induced to the recombinant clostridium toxins.

It would have been obvious to the person of ordinary skill at the time the invention was made to modify the recombinant polypeptide instantly claim with the polyhistidine tract of Williams et al because Williams et al teaches and shows the successful production of recombinant clostridium toxins and teaches prokaryotic expression systems for the attainment of recombinant Clostridial toxins through expression of single polypeptide chains, wherein the single polypeptide chains will bind

to a ligand containing column to aid in protein isolation and purification, the polypeptides including either a maltose binding protein or a polyhistidine tract polypeptide tag (pET16b) (see Example 11, column 35), and these methods serve to define means for attainment of high levels of recombinant toxin.

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a botulinum C-terminal portion recombinant protein that comprises a polyhistidine tract utilizing the expression system because Williams successfully shows the recombinant expression of a Clostridial toxin using a polyhistidine tract polypeptide which provides the advantage of attaching the polypeptide polyhistidine tract either at the C-terminal end (pET23a-c) or the N-terminal end (pET16b) (see Example 11, col. 35, lines 26-49) of the Clostridial polypeptide depending on the preferred location of the non-toxin polyhistidine tract polypeptide.

Double Patenting-Overcome and withdrawn

5. The former double patent rejection of claims 25-26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 9,12-14 of U.S. Patent No. 6,787,517 has been overcome by the filing of a Terminal Disclaimer.

The former rejection of claims 25-30 as being directed to the same invention as that of claim 10 of commonly assigned 5,919,665 has been withdrawn. The claims are not claiming the same invention since the instant claims do not recite fusion proteins comprising a C fragment of C.botulinum linked to a poly-histidine tag.

6. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile

transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

JGraser

Jennifer Graser 4/12/06
Primary Examiner
Art Unit 1645